**Questionnaire/Survey Data**
**Candace Adams**

- Sample size inconsistencies: discrepancies in numbers of subjects entering the study, the number of dropping off from the study as well as the number of subject included into final statistical analyses (33 participants were ineligible, 22 of 33 (73%) provided evidence of ineligibility at enrollment).
- Request revised report using 107 respondents who complied with protocol.
- Examine the "monitoring report" to find out why the patient were not excluded from the study when there was an evident violation of inclusion criteria.
- Request diary information from Covance.
- Review Covance`s note re: refusals and requests for clarification on specific question items (p.48)
- The demographic part of the report is abbreviated. (it should also includes table of different brand cigarettes smoked, smoking behavior,..... )
- Implement intra-subject variability among leisure and non leisure days



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was incorrect, e.g. there was no enzyme preparation for further analysis, also the storage does not meet the standard conditions.

- All sputum samples should be destroyed.
- False statement at Pg 83, 2nd last sentence – "All the biomarkers, with the exception of HDL-cholesterol, had higher levels in non-smokers than smokers. Should we read".... Higher levels in smokers than non-smokers."
- Phenotyping (CYP1A2, NAT2) need distribution and probit analysis. The clarification of the definition for "slow" and "not slow" NAT2 activity has to be done. Substitute those terms for "high" and "low" NAT2 activity.
- Page 89 line 6 – "CYP1A2 also seemed to be a good predictor for many biomarkers of exposure. This is not an accurate statement.
- Analyze the correlation between phenotyping and biomarkers of effect. Calculate a simple relationship - biomarkers vs CYP1A2 and NAT2: 3,4-ABPHb adducts vs CYP1A2, Cotinine vs CYP1A2, or nicotine/cotinine ratiovs CYP1A2, Trans-Cot +cotinine/nicotine ratio vs CYP1A2, NNAL vs NAT2
- Drop off acetonitrile data from the analysis in the subsequent large study, negligible correlation found in concentration of acetonitrile to amount of cigarettes, box plot Pg 7952 shows lot of outliers both in smokers and nonsmokers.
- NNAL and metabolite assay needs to be set up and validated. Considering 41% assay variability very little meaningful conclusion can be made.
- LOQ values should be remembered when reporting significant figures
- There are large discrepancies among the 3&4-ABP-Hb adducts values between INBIFO and COVANVE lab.(e.g. INBIFO 60pg/g vs COVANCE 15pg/g). Need to be determine which method is more reliable. Decide whether we are going to exclude 3-ABP-Hb from further analysis, or should be keep it for quality check. (in case we need to check on outliers for 4-ABP-Hb)
- Clarify the term "nicotine plus 5 metabolites". Substitute the whole term for "nicotine equivalents and clearly define what we mean by that.
- Synchronization of the units throughout the whole report is required. Also decision about up to what decimal analytical data should be presented.



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